**Family Planning and Reproductive Health Methods to Address Unmet Need**

**USAID Cooperative Agreement:**
7200AA20CA00016

Innovate FP

Expanding Options, Enhancing Method Choice

# Year 3 Workplan

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THE SCIENCE OF IMPROVING LIVES

## Introduction

The goal of Innovate FP is to expand desirable, affordable, quality contraceptive options to enable women to better meet their changing needs and desires throughout their reproductive lives. The proposed research agenda aligns with three of the specific aims outlined in the original USAID Annual Program Statement: 1) refine existing methods to address method-related reasons for non-use; 2) respond to product-related issues about existing methods; and 3) develop new methods that address method-related non-use and/or fill gaps. Strengthening current and building new partnerships are key to advancing the aims of Innovate FP.

The following sections define the proposed workplan for Year 3 of Innovate FP (October 1, 2022– September 30, 2023). The corresponding budget for these activities, presented for the third year of the project and for the estimated life of project, is provided in Appendix 1.

### *AIM 1: Refine existing contraceptive methods*

Our focus under Aim 1 is to refine and advance knowledge on mid- to long-acting contraceptives, with a specific focus on extending duration and lowering the overall dose of depot medroxyprogesterone acetate (DMPA) injectables. The highest priority is implementing a safety and effectiveness trial of a 6-month DMPA product.

#### *6-month DMPA SC (DMPA XT): pivotal Phase 3 trial*
#### *Lead: Vera Halpern, MD*

*The UK sites are funded by the study product manufacturer.*

***Goal**:* To conduct a pivotal Phase 3 trial for stringent regulatory approval of a 6-month subcutaneous (SC) contraceptive injectable (DMPA XT) based on an existing, generic 3-month DMPA intramuscular (IM) formulation.

***Significance and Impact*:** Over 40 million women worldwide use injectable contraceptives, including more than one-third of modern method users in sub-Saharan Africa. Current injectables are effective for one to three months, requiring relatively frequent visits for re-injection. However, recent research has documented that many women would prefer injectables that last longer, in part for convenience. Under *Envision FP (*USAID Cooperative Agreement AID-OAA-A-15-00045), with co-support from the Bill & Melinda Gates Foundation (BMGF), FHI 360 showed that a single SC injection of 3-month DMPA IM (150 mg) suppresses ovulation completely for at least 7 ½ months while reducing dose by half when compared with the current 3-monthly IM regimen. These data provided proof-of-concept that a novel 6-month injectable could be brought to market in a rapid, cost-efficient manner by repurposing an existing DMPA IM product. We also received scientific advice from two European national regulatory agencies and an endorsement of a Phase 3 trial design and regulatory development plan.

With positive study results from a pivotal Phase 3 trial, DMPA XT could be approved as early as 2025/26 by a European regulatory agency, far ahead of other 6-month injectables currently in development. The new product will use the same 150mg/mL vial as the 3-month DMPA IM formulation and will be co-packaged with an SC syringe. This will keep manufacturing costs low and contribute to a substantially shorter time to market.

***Approach:*** We will enroll up to 750 women (at least 25% of them in Europe) willing to use DMPA XT every 6 months as their only means of contraception for 12 months and evaluate efficacy, safety, bleeding changes, and acceptability. Additional important aspects of this study will be to: 1) assess the impact of this lower-dose strategy on bone mineral density; and 2) characterize how pharmacogenomic differences among participants (particularly certain genetic variants) may influence side effects or outcomes. Major milestones include: 1) enrollment completion (Q4 Yr 3); 2) interim analysis when 50% of participants complete 12 months (Q4 Yr 3); 3) follow-up completion (Q2 Yr 5); 4) final analysis and clinical study report (Q4 Yr 5).

We bring a substantial financial commitment (co-funding and clinical supplies for the trial) from a pharmaceutical company with a WHO-prequalified DMPA IM product and interest in marketing DMPA XT in FP2020 countries. Using their 3-month DMPA IM formulation currently being procured by USAID, we will leverage their WHO PQ dossier to accelerate the clinical trial application (CTA) preparation and study start-up. We will seek an eventual marketing authorization in an EU member country via a hybrid generic application under the decentralized procedure and will develop a product registration and introduction strategy for FP2020 countries during the pivotal trial. We will seek additional funding from other commercial partners, as appropriate, for regulatory submissions and roll-out in non-FP2020 markets/countries if the trial is successful.

***Year 3 Workplan:*** We expect to receive additional scientific advice on various regulatory questions related to our DMPA-XT product development plans from the Swedish Medical Products Agency (MPA) in Oct. 2022.

We plan to receive protocol approval and import clearance in Oct. 2022 from the Chilean regulatory authority, Insituto de Salud Publica, and will initiate recruitment at ICMER (Chile) shortly thereafter, with enrollment continuing throughout the year. Profamilia (Dominican Republic) and MatCH (South Africa) sites will continue enrolling participants through Jul. 2023 and Jan. 2023, respectively, if they meet the current monthly enrollment targets.

Clinical monitors will conduct periodic interim monitoring visits at all study sites. We will perform ongoing centralized monitoring of site performance, data collection and protocol compliance throughout the year.

We plan to execute a subcontract with a central PK laboratory in Nov. 2022, and initial PK samples will be analyzed in Aug. 2023 in preparation for the scheduled interim analysis based on approximately 250 subjects reaching 6 months of follow up.

Using funds from the Investigational Medicinal Product manufacturer, we will execute clinical trial agreements with Chalmers Centre and The Gatehouse (United Kingdom), conduct site initiation training, and initiate recruitment in the UK in Oct. 2022.

***Year 3 Implementation Timeline***

| Innovate FP Year Three Work Plan October 1, 2022 - September 30, 2023 | 2022 | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Regulatory approvals | • | | | | | | | | | | | |
| Initiation training and activation of trial sites | • | | | | | | | | | | | |
| Interim Analysis | | | | | | | | | | | • | |
| Centralized and on-site monitoring | • | • | • | • | • | • | • | • | • | • | • | • |

***DMPA SC Extended use: user and service delivery considerations***

***Leads: Holly Burke, PhD and Rebecca Callahan, PhD***

*This study is co-funded by the Children's Investment Fund Foundation (CIFF). CIFF is funding the two sites (Uganda and Nigeria).*

***Goal***: To evaluate and understand market implications, including user, provider, and other stakeholder perspectives, on adding multiple extended DMPA SC products to the method mix.

***Significance***: Understanding the market implications of adding new injectables of varying durations and delivery mechanisms into programs within a similar timeframe is essential to provide an evidence-based roadmap for successful product introduction. This work will complement and expand a scoping activity funded by CIFF to develop a regulatory strategy and explore the market implications of introducing multiple injectable products. Limited qualitative research has explored provider and other stakeholder perspectives on introducing injectables of varying durations. More data are needed, including from users, in varying contexts to inform introduction decisions.

***Approach***: We will use multiple methods including qualitative interviews and human-centered design (HCD) research and workshops to solicit user and stakeholder opinions, preferences, and suggestions on the prospect of introducing both a 4-month DMPA SC in Uniject and a 6-month DMPA SC injectable (syringe and vial; DMPA XT) to the method mix. For Activity 1, we will conduct in-depth interviews with FP providers, program implementers, policy makers, and others in Nigeria and Uganda to explore opportunities, challenges, and preferences for the introduction of multiple new injectable products. For Activity 2, we will conduct triads (discussions with 3 participants) with males/partners, mini focus group discussions (FGDs) (up to 5) with users and facilitate HCD workshops with potential users to explore preferred approaches for providing different duration injectables and types. The workshops will also be used to generate communication strategies and marketing messages for these new products.

***Year 3 Workplan:*** A second manuscript, focused on provider and other key FP stakeholder perspectives on the introduction of new injectables of varying durations (4 and 6 months), will be drafted and submitted to USAID for review by the start of Year 3. Planned work on this activity in Year 3 includes making any necessary revisions to the manuscripts and conducting in-country dissemination events in Nigeria and Uganda. These events will be led by site investigators in each country and will bring together program, policy, and service delivery stakeholders to share the results of the research.

## *AIM 2: Respond to product-related issues about existing contraceptive methods*

Under *Envision FP*, FHI 360 successfully addressed a wide variety of product-related issues that had potential to create barriers to availability and use. We will use a similar Rapid Response approach under Innovate FP.

### *Rapid response and proactive risk mitigation for contraceptive programs*
### *Leads: Markus Steiner, PhD and Elena Lebetkin, MPH*

***Goal:*** To address product-related issues in the field that affect provider/user perceptions, policies, programs, and/or the supply chain.

***Significance and Impact*:** When concerns about contraceptives arise in the field, loss of trust can quickly lead to dramatic disruptions in contraceptive procurement, programs, and use. The rapid response activity supports evidence-based policies and programs by dispelling rumors, quelling anxiety, and filling information gaps.

***Approach**:* Innovate FP will continue and strengthen our successful Rapid Response mechanism, drawing upon a multidisciplinary team of experts from FHI 360, including our Product Quality and Compliance (PQC) team and our partners, to rapidly and systematically respond to field-based concerns as well as to proactively identify and address issues. Our approaches will include literature reviews, evidence synthesis, data analysis and modeling, document review, new tool development, and product quality assurance. We will also support systematic reviews on product-related issues focusing on topics with direct relevance to our product development portfolio. We will leverage our country offices and work closely with USAID, MOHs, and local partners to address field concerns collaboratively. We will make every effort to work directly with field-based partners in order to build capacity to respond to concerns locally.

***Year 3 Workplan:*** The team will continue passive surveillance to review field concerns identified by USAID and propose proactive responses using the collaborative approach with USAID colleagues. We will continue to closely monitor the COVID-19 pandemic threats to global contraceptive services and supply chains, and we will proactively engage with service delivery partners, manufacturers, and other stakeholders to evaluate situations that may merit engagement with our team to mitigate risk and maintain safe services and practices. We will also explore the need for product briefs and systematic reviews related to product development in discussion with USAID. Finally, we will continue work on the ongoing activities as described below.

**Uniject malfunction**

We will continue monitoring for reports of Uniject malfunction and, if reports are received, we will work with USAID to determine the appropriate response strategy and interface with the manufacturer (Pfizer) as appropriate.

**Caya Diaphragm**

The team will continue to have conversations about the contraceptive gel to be used with the Caya diaphragm and potential ways to bring the price of Caya gel to a more affordable level.

**CONRAD trocar**

Steiner will follow up with CONRAD to determine TA needs and will provide TA as requested.

**Contraceptive Technology chapters**

Steiner will continue working on chapter revisions as requested by the editor with an anticipated finalization in the first quarter of Year 3. The team will disseminate the work and engage with the Family Planning Global Handbook authors to ensure that information aligns across the new version of both Contraceptive Technology and the Global Handbook (when the next version is released).

**Return to fertility technical review**

The team will finalize the manuscript and submit to a peer reviewed journal in quarter 1 of Y3.

**Couple Year Protection (CYP) manuscript**

The team will finalize a manuscript which details the process used to develop the updated CYP factors and will submit the manuscript to a peer reviewed journal in quarter 1 of Y3.

***Year 3 Implementation Timeline***

| Innovate FP Year Three Work Plan<br>October 1, 2022 - September 30, 2023 | 2022 | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Passive surveillance for field-generated concerns | • | • | • | • | • | • | • | • | • | • | • | • |
| Respond to USAID requests/field-generated concerns | • | • | • | • | • | • | • | • | • | • | • | • |
| Develop product briefs in consultation with USAID | • | • | • | • | • | • | • | • | • | • | • | • |
| Monitor need for response due to COVID-19 | • | • | • | • | • | • | • | • | • | • | • | • |
| Explore need for systematic reviews | • | • | • | • | • | • | • | • | • | • | • | • |
| Monitor for Uniject malfunctions | • | • | • | • | • | • | • | • | • | • | • | • |
| Draft CYP manuscript & submit to journal | • | • | • | | | | | | | | | |
| Provide trocar TA to CONRAD, if requested | • | • | • | • | • | • | • | • | • | • | • | • |
| Provide Caya diaphragm regulatory strategy input | • | • | • | • | • | • | • | • | • | • | • | • |
| Revise chapter 5 of *Contraceptive Technology* | • | • | • | | | | | | | | | |
| Complete Return to Fertility technical review | • | • | • | | | | | | | | | |

***Addressing contraceptive-induced menstrual changes in contraceptive R&D***
***Leads: Amelia Mackenzie, PhD and Rebecca Callahan, PhD***

*Work related to the CIMC Global RLA and CIMC Task Force is co-funded by Research for Scalable Solutions (R4S).*

***Goal:*** To ensure that potential contraceptive-induced menstrual changes are adequately addressed in contraceptive research and development.

***Significance and Impact**:* Contraceptive-induced menstrual changes impact users' lives in both positive and negative ways. CIMCs can be a reason that individuals are dissatisfied with, discontinue, or avoid using hormonal methods and copper IUDs. At the same time, insufficient attention is often paid to the variety of non-contraceptive health benefits of contraceptives, such as the potential to treat or manage symptoms of menorrhagia, dysmenorrhea, endometriosis and/or other menstrual disorders, as well as to prevent or reduce the risk of iron deficiency anemia and other health outcomes. Reduced bleeding or amenorrhea can also have lifestyle advantages for some women such as increased freedom to engage in work or school activities and/or reduced costs associated with menstrual hygiene products. Consideration of CIMCs and other non-contraceptive benefits needs to be integrated into contraceptive R&D efforts as new products are being developed, evaluated, and introduced.

***Approach**:* Under Innovate FP, our team will leverage ongoing work by FHI 360 and others to support product developers, donors, national governments, and other key stakeholders to ensure that potential CIMCs and other non-contraceptive health benefits are adequately addressed in contraceptive research and development. This work builds upon thought leadership under *Envision FP* including a technical consultation on CIMCs that took place in Nov. 2020 in collaboration with the USAID-funded Research for Scalable Solutions (R4S) project.

***Year 3 Workplan:*** We will continue to advance and disseminate the CIMC Global Research and Learning Agenda (RLA) at relevant convenings and forums, including at the 2022 International Conference on Family Planning, the UNC Water and Health Conference, Reproductive Health Supplies Coalition meetings, in addition to other venues. With co-funding from R4S, we will convene the CIMC Task Force in Year 3 and will continue to focus on developing technical content and resources, as well as promoting the resources developed in Year 2 and reaching out to implementing partners to encourage uptake, adaptation, and piloting of these new resources. The project team will complete and submit for publication the systematic review of measures of changes to the menstrual cycle and will organize and convene an expert consultation to develop recommendations for measuring and analyzing CIMCs in contraceptive clinical trials. Recommendations from this consultation will then be submitted for publication. We will also develop a regulatory engagement strategy to incorporate the perspectives of regulators into future work emanating from the recommendations, including identifying upcoming product-specific meetings with the FDA for products in the FHI 360 pipeline, during which we can inquire about measuring and analyzing CIMCs in the context of clinical trials. In addition to these activities, we will continue thought leadership within the CIMC arena and explore future avenues on the connections between CIMCs and non-contraceptive benefits (e.g., anemia reduction and sexual health and wellness).

***Year 3 Implementation Timeline***

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Disseminate CIMC Global RLA | • | • | • | • | • | • | • | • | • | • | • | • |
| Convene CIMC Task Force | • | • | • | • | • | • | • | • | • | • | • | • |
| Complete systematic review | • | • | • | • | | | | | | | | |
| Plan expert consultation | • | • | • | • | | | | | | | | |
| Convene expert consultation | | | | • | | | | | | | | |
| Submit systematic review manuscript | | | | | • | | | | | | | |
| Complete expert recommendations manuscript | | | | | | • | • | • | | | | |

## ***Leading Global- and Country-Level Coordination of Hormonal IUD Scale-Up***
## ***Lead: Andrée Sosler***

***Goal:*** Support introduction and scale-up of affordable, quality-assured hormonal IUD products in the context full method choice.

***Significance and Impact****:* The hormonal IUD is one of the most effective forms of reversible contraception with important non-contraceptive benefits. Until recently, the method has not been widely available in low-resource settings, but the global landscape is changing, and two quality-assured hormonal IUD products have recently been added to the USAID and UNFPA product catalogs. Now, governments in several countries are moving to scale up the method, and FHI 360 is collaborating with partners and donors to facilitate broader availability and access in the context of volunteerism and full method choice.

***Approach****:* The team will provide technical leadership and coordination to support the introduction, scale-up and evaluation of the hormonal IUD in LMIC settings.

***Year 3 Workplan:*** FHI 360 will serve as co-Secretariat of the Hormonal IUD Access Group which will include co-coordination of the Steering Committee, the Operations sub-committee, and the Partners Exchange. In this role, FHI 360 will also help manage coordination and strategic planning with the SEMA Reproductive Health platform. On the supply-side, FHI 360 will collaborate with CHAI and the PSM-GHSC project to provide technical assistance to Medicines360 to help facilitate a potential technology transfer to increase product affordability and access in LMICs.

FHI 360 will also continue to support coordination for hormonal IUD introduction including sharing updates with global stakeholders about progress in Phase I countries (e.g., Nigeria, Kenya, Rwanda, etc.) as well as status in Phase 2 countries (e.g., Uganda, etc.). FHI 360 will also continue to manage and expand content on the Hormonal IUD Access Portal website (https://www.hormonaliud.org/).

***Year 3 Implementation Timeline:***

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Serve as co-Secretariat of the Hormonal IUD Access Group | • | • | • | • | • | • | • | • | • | • | • | • |
| Provide technical assistance to Medicines360 to help facilitate a potential technology transfer | • | • | • | • | • | • | • | • | • | • | • | • |
| Support country coordination in Phase 1 & 2 countries | • | • | • | • | • | • | • | • | • | • | • | • |
| Manage content on the Hormonal IUD Access Portal | • | • | • | • | • | • | • | • | • | • | • | • |

## *AIM 3: Develop new contraceptive methods to address method-related non-use and/or fill gaps*

FHI 360 and its partners have made significant progress toward the development of novel, long-acting progestin-only contraceptive products including a microneedle patch (MNP) and a biodegradable implant (BDI). Under Innovate FP, we will continue to advance these two products, leveraging funding from other donors. Parallel acceptability research will inform formulation and design decisions.

### *A 3-6 month progestin-only microneedle patch*
### *Lead: Jennifer Ayres, PhD*

***Goal****:* To develop a discreet, user-initiated long-acting progestin-only microneedle patch (MNP) contraceptive.

***Significance and Impact***: While a variety of progestin-only contraceptives are popular worldwide, additional easy-to-use innovative options could expand choice, improve continuation, and reduce unmet need. Progestin-containing biodegradable MNP delivery systems would offer women truly innovative, discreet contraception allowing simple and safe self-administration without biohazardous waste. Unlike current contraceptive patches which remain in place, after the MNP is applied, the backing is quickly removed, leaving the biodegradable microneedles embedded in the skin to deliver their payload.

***Approach:*** Under *Envision FP*, we collaborated with Dr. Mark Prausnitz (Georgia Tech) to use his MNP platform to directly load progestin into *slowly* biodegradable microneedles for 3-6 months contraceptive coverage. [Note: This work leveraged parallel BMGF-funded activities to develop MNPs with *rapidly* dissolving microneedles containing progestin-loaded microparticles for 6 month contraception.] We evaluated LNG, etonogestrel (ENG) and nestorone (NES) for formulation compatibility. LNG has greater compatibility with the fabrication process and yielded slower release kinetics due to its lower solubility in both organic and aqueous media. NES has the greatest solubility and was determined to be incompatible with extended release

from MNPs, so development activities were discontinued. ENG has intermediate solubility. We selected LNG for further development; however, we will continue some activities with ENG. We are considering ENG as a back-up active pharmaceutical ingredient (API) and ongoing activities will provide information on how API structure and solubility affect microneedle properties and release characteristics.

A 3-6 month MNP for women will need to be larger and contain more needles and/or larger needles than those used in the rat in order to deliver a greater amount of drug. Under *Envision* FP, Georgia Tech conducted a human placebo patch study of 18 MNP designs to evaluate pain and acceptability with rapidly dissolving microneedles varying in number, size and spacing to inform the maximally tolerable limits for these parameters. Under Innovate FP, Georgia Tech will collaborate with Emory University and FHI 360 to conduct a trial to evaluate the safety, tolerability, and biodegradation of placebo MNPs with a slowly biodegradable needle formulation to further inform formulation development as well as the longer-term safety of the slowly biodegradable system (something not assessed in the study of rapidly dissolving MNP designs). We will evaluate approaches to maximize drug loading and control release kinetics while designing patches suitable for human dosing. Georgia Tech will conduct a series of smaller placebo studies to evaluate pain, acceptability, and delivery efficiency of rapidly dissolving needles to inform the feasibility of multiple designs for larger patches. They will also do iterative *in vitro* dissolution and rat PK studies to optimize the formulation. After selecting a lead candidate for human dosing, we will engage a CRO to conduct a study to evaluate LNG MNP application and PK in a mini-pig model with skin and subcutaneous tissue similar to humans to inform dosing for a Phase 1 trial. We will work with a regulatory consultant to define the scope of pre-Investigational New Drug (IND) activities, have a pre-IND meeting with the U.S. Food and Drug Administration (FDA), and work with a CRO to conduct the recommended IND-enabling studies. Based on the extensive prior use of LNG and excipients utilized in these formulations, we believe minimal toxicology studies will be required. We will seek additional funding to support a Phase 1 trial.

***Year 3 Workplan:*** The team at Georgia Tech will complete manufacturing of patches for the placebo clinical study and work with Emory to initiate the study in Feb. 2023. They will initiate a series of rat PK studies to evaluate prototype core-shell MNPs and inform formulation and process optimization. They will also complete process development for making core-shell MNPs using the Biospot nanodispensing instrument and select the approach that will be used for further development (solvent casting vs. nano-dispensing) before continuing optimization and characterization of the core-shell MNP. The Georgia Tech team will also continue the development of larger MNP designs to accommodate sufficient dosing for the target 3-6 month duration. In parallel, they will optimize the design of application tools in case these are needed for the larger patch designs. They will continue to evaluate the effects of gamma sterilization on MNP formulations and evaluate preliminary stability for both irradiated and non-irradiated prototypes. The team at the University of Michigan will continue studies to evaluate the mechanism of LNG release from MNPs both in vitro and in vivo to inform formulation development. We will submit an updated TPP in Feb. 2023 and an updated IPDP in Jun. 2023. Once data are available for both the placebo study and the rat PK study to evaluate the core-shell MNP, we will conduct an External Review Committee Meeting to review updated project data and overall program strategy.

***Year 3 Implementation Timeline***

| Innovate FP Year Three Work Plan<br>October 1, 2022 - September 30, 2023 | 2022 | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Manufacture patches for placebo study | • | • | | | | | | | | | | |
| Sterilize and conduct sterility testing for placebo patches | | • | • | | | | | | | | | |
| Conduct placebo study to evaluate safety, tolerability, and biodegradation of MNPs (slowly biodegradable needles) | | | | | • | • | • | • | • | • | • | • |
| Conduct rat PK studies for prototype core-shell LNG patches | • | • | • | • | • | • | • | • | • | • | • | • |
| Continue process development for core-shell MNP fabricated with Biospot nanodispensing equipment | • | • | • | | | | | | | | | |
| Finalize process for making core-shell MNPs (solvent casting vs. Biospot) | | | | • | | | | | | | | |
| Continued optimization and *in vitro* release testing for core-shell LNG patch | • | • | • | • | • | • | • | • | • | • | • | • |
| Design and characterize larger MNP designs | • | • | • | • | • | • | • | • | • | • | | |
| Optimize design of MNP Application Tools | • | • | • | • | • | • | • | • | • | • | | |
| Evaluate effects of radiation sterilization on LNG patches | • | • | • | • | • | • | • | • | • | • | • | • |
| Conduct preliminary stability testing for LNG patches | • | • | • | • | • | • | • | • | • | • | • | • |
| Continue study to evaluate mechanisms of LNG release from MNPs *in vitro* and *in vivo* | • | • | • | • | • | • | • | • | • | • | • | • |
| Submit TPP to USAID | | | | | • | | | | | | | |
| Submit IPDP to USAID | | | | | | | | • | | | | |
| External Review Committee Meeting | | | | | | | | | | | | • |

***A 18-24 month biodegradable implant***
***Lead: Jennifer Ayres, PhD***

*This activity is co-funded by the Bill and Melinda Gates Foundation.*

***Goal:*** To accelerate prototype development and shorten the timeline for a first in human (FIH) trial of an LNG Biodegradable Implant (BDI) with a duration of 18 to 24 months.

***Significance and Impact:*** Existing contraceptive implants require removal, which necessitates trained personnel, supplies, and equipment that are often limited in low-resource settings. A BDI would expand choice and provide an innovative option to reduce the removal challenges and burden for users and providers/clinics.

***Approach:*** Since 2014, FHI 360 has collaborated with Dr. Mark Saltzman (Yale University) to develop a BDI, with support from USAID and BMGF. This approach utilizes a novel copolymer, poly(ω–pentadecalactone-co-pdioxanone) [poly(PDL-co-DO)], with hydrophilic and hydrophobic components, the ratio of which can be tuned to optimize API release and duration. This copolymer remains mechanically strong over time, an important consideration for removability if desired by the user. The target product profile (TPP) for this product includes an intermediate

duration of effectiveness (18-24 months), removability for up to 6 months before the intended duration, and a short tail (preferably less than 6 months) for a predictable return to fertility. To date, we have developed methods for manufacturing LNG BDI implants on a small scale and evaluated formulation and process parameters *in vitro* and *in vivo* to optimize release kinetics. For candidate formulations, we have demonstrated biocompatibility in mice (6 months) and sustained release and removability in rats (20 months). We further optimized implant designs to minimize the release tail (inactive copolymer core/progestin shell design) and the initial burst (inactive coating). With BMGF support, we will continue formulation optimization which will be informed by *in vitro* dissolution studies to characterize LNG release, by experiments to measure polymer degradation and implant strength as a function of incubation time (*in vitro*), and by preliminary sterilization feasibility and stability testing.

Under Innovate FP, we will leverage this BMGF-funded work to maximize the likelihood of success and accelerate the timeline to the clinic. Activities will include:

1. Optimization and scaling of both the polymer and implant manufacturing processes: Both polymer and implants are currently fabricated on a lab scale which is not viable for the clinical trial product. We have scaled up the polymer manufacturing process at Polysciences and will develop a scalable implant fabrication process at Lubrizol with the potential to support Phase 1 clinical trial manufacturing and associated stability programs.

2. Toxicology studies to support regulatory filings: Based on feedback from a Type C meeting with the FDA, we plan to conduct biocompatibility testing per ISO 10993-1 on the combination product in its final finished form, including cytotoxicity, intracutaneous irritation, sensitization, acute systemic toxicity, material-mediated pyrogenicity and subacute/subchronic systemic toxicity before the FIH trial. The FDA indicated that we would also need to conduct chronic toxicity, genotoxicity, carcinogenicity, and reproductive/development toxicity testing but that a comprehensive chemical analysis followed by a toxicological risk assessment may be used as an alternative to these studies. We will confirm with the FDA that these additional tests are not needed prior to FIH and can be conducted at later stages of development to support an NDA submission, as typical in most drug development programs.

3. Additional animal studies: We will conduct a rat PK study with core-shell implants with biodegradable cores manufactured using the scalable manufacturing process at Lubrizol. Prototypes for this study will be informed by accelerated dissolution data and release modeling. Based on data collected through six months, we will make a go/no-go decision to move to further process scale-up and toxicology. The rat PK study will continue to 24 months in parallel with these activities.

***Year 3 Workplan:*** We will continue work with Lubrizol to develop a co-extrusion process for manufacturing core-shell implants and will evaluate feasibility for two different core materials. Once optimization and qualification of the gel permeation chromatography (GPC) method used to measure polymer molecular weight is complete (this activity supported by BMGF), the team at Yale will manufacture implants for microstructural analysis and LNG release modeling at DigiM, which will be conducted at multiple timepoints during *in vitro* dissolution testing. We will initiate a rat PK study to evaluate core-shell implants manufactured at Lubrizol and make a Go/No-Go decision to continue to GLP toxicology and process scale-up based on 6-months of data. Once data are available, we will conduct an External Review Committee meeting to

review recent data and overall program strategy. In Feb. 2023, we will submit an updated TPP and IPDP.

With BMGF-funding, we will work with Polysciences to complete the optimization and qualification of the GPC method, so that we have confidence in molecular weight measurements for all future experiments. The team at Yale will continue *in vitro* dissolution studies for implants with stainless steel cores to determine whether there are inherent differences in release for the formulations evaluated in the rat PK study compared to those with biodegradable cores. They will also continue to evaluate accelerated dissolution assays at 50 °C and 60 °C. Preliminary experiments indicated that implants fabricated with low molecular weight and/or high LNG loading were brittle. As such, the Yale team will modify their implant fabrication methods to improve mechanical properties for these samples before conducting experiments to evaluate the effects of polymer molecular weight and LNG loading on release kinetics. Current implants have a shell containing 28% LNG; higher drug loadings could facilitate manufacture of smaller implants. They will evaluate the effects of gamma radiation on implant properties and release kinetics and then initiate stability testing at 25 °C and 40 °C for both irradiated and non-irradiated prototypes. The current BMGF grant (CTII-2) ends in Dec. 2022, and continuation of this work beyond this date is dependent upon receipt of additional funding; discussions with the foundation are ongoing and a decision about funding for the next phase is pending.

***Year 3 Implementation Timeline***

| Innovate FP Year Three Work Plan<br>October 1, 2022 - September 30, 2023 | 2022 | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Funded by Innovate FP | | | | | | | | | | | | |
| • Continue process development and optimization activities with Lubrizol | • | • | • | • | | | | | | | | |
| • Manufacture implants for microstructural analysis | • | • | | | | | | | | | | |
| • Work with DigiM to characterize implant microstructure at multiple timepoints | | • | • | • | • | • | • | • | | | | |
| • Initiate rat PK study for implants manufactured at Lubrizol | | | | | | • | • | • | • | • | • | • |
| • Decision to move to GLP toxicology and scale-up | | | | | | | | | | | | • |
| • Submit TPP to USAID | | | | | • | | | | | | | |
| • Submit IPDP to USAID | | | | | • | | | | | | | |
| • External Review Committee Meeting** | | | | | | | | | | | | • |
| Funded by BMGF* | | | | | | | | | | | | |
| • Optimize and qualify GPC method for molecular weight determination | • | | | | | | | | | | | |
| • *In vitro* dissolution for implants in PK study (IVIVC) | • | • | • | • | • | • | • | • | • | • | • | • |
| • Continue evaluation of accelerated dissolution assays | • | • | • | • | • | • | • | • | • | • | • | • |
| • Modify implant fabrication method to accommodate implants with lower molecular weight and higher drug loading | • | • | • | | | | | | | | | |
| • Evaluate the effects of polymer molecular weight on implant properties and LNG release kinetics | • | • | • | • | • | • | • | • | • | • | • | • |
| • Evaluate implants with higher LNG loading | • | • | • | • | • | • | • | • | • | • | • | • |
| • Evaluation of gamma sterilization | • | • | • | • | • | • | • | • | • | • | • | • |
| • Preliminary stability evaluation | | | • | • | • | • | • | • | • | • | • | • |

**For reference we have provided information on Innovate FP in this table, as well as the leveraged BMGF-funded activities. The current BMGF grant (CTII-2) ends in Dec. 2022. Activities listed in the timeline beyond this date are dependent upon receipt of additional funding.*

***We anticipate that this activity will also be supported by BMGF.*

***Market research on novel contraceptive BDIs among providers and potential users***
***Lead: Rebecca Callahan, PhD***

*This study is being co-funded by the Bill and Melinda Gates Foundation (BMGF). BMGF is funding the two sites (Senegal and Kenya). USAID funds are being used to support Senegal non-site activities.*

***Goal:*** To explore end-user, provider, and other stakeholder perspectives on a Biodegradable Implant (BDI) to inform product messaging and introduction.

***Significance and Impact:*** End-user preferences, attitudes, and concerns can inform product development decision-making as well as help plan for eventual product introduction. In 2015, FHI 360 led an assessment of user perspectives on six new contraceptive products under development, including a generic BDI. Limited data from this study indicated that some women and family planning providers have apprehensions about the biodegradable nature of the product, including concerns about safety and what happens to the implant when it biodegrades. Although this study provided some insights into the potential acceptability of a generic BDI, because it focused on multiple novel products, we were unable to deeply explore user and provider reactions specific to a BDI. Under Innovate FP we will conduct a dedicated study to explore user, provider, and male/partner perspectives for a contraceptive BDI, including the desired duration of action and acceptable period of non-removability, and explore product characteristics unique to two BDI products in our pipeline. These data will also inform future introduction and communication messaging. The data collected will inform BDI development programs funded by USAID and others.

***Approach:*** This research will focus on the TPPs of the two BDIs in FHI 360's current pipeline. We will also explore with CONRAD opportunities to incorporate relevant questions about the BDI in their portfolio. We will conduct qualitative research in two countries, determined in collaboration with USAID. Factors considered during country selection included contraceptive method mix including implant use prevalence, public and private sector support for new contraceptive product introduction, and USAID Mission interest in the research project. We will carry out focus group discussions (FGDs) with women and interviews with family planning providers and other stakeholders including Ministry of Health officials and FP program managers to explore perspectives on product attributes, service delivery considerations such as removability, and potential introduction opportunities and challenges. With both users and providers/stakeholders we will explore the biodegradable nature of the product and solicit input on how best to describe the product to inform future marketing and messaging efforts.

***Year 3 Workplan:*** Data collection for this study will be complete by Oct. 2022. Between Oct. 2022 and Feb. 2023, we will complete data analysis and manuscript writing. We will share results with USAID, BMGF, and BDI product developers at Yale and pH Sciences, and conduct in-country dissemination events with co-funding from BMGF. Results of the study will also be shared via poster presentation at the International Conference on Family Planning meeting in Thailand in Nov. 2022.

***Year 3 Implementation Timeline***

| Innovate FP Year Three Work Plan<br>October 1, 2022- September 30, 2023 | 2022 | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | O | N | D | J | F | M | A | M | J | J | A | S |
| Complete data analysis | • | • | • | | | | | | | | | |
| Manuscript writing | • | • | • | • | • | | | | | | | |
| ICFP presentation | | • | | | | | | | | | | |
| Dissemination events | | | | • | • | | | | | | | |

## *Project Management and Monitoring, Evaluation & Learning*

### *Lead: Amanda Troxler; Operations Manager*

In an effort to ensure that Innovate FP project activities are completed on time and within budget, FHI 360 has a centralized hub of operations for project management as well as monitoring, evaluation, and learning. These functions work together to serve as a feedback loop for the status of individual activities in support of project planning and reporting requirements as well as to identify opportunities for learning and project efficiency.

Project management is provided at both the specific activity and overall project levels. Innovate FP project management is responsible for ensuring that all award and reporting requirements to USAID are met and will serve as a liaison between USAID and the activity-level project managers, communicating issues related to timeline and budget. The Innovate FP project management team will submit international travel plans to USAID for approval. In addition, the team developed a policy compliance plan and shared with USAID. The team also worked with gender experts at FHI 360 to develop a gender strategy, which was approved by USAID. For any activity that requires mission concurrence, Innovate FP project management will work with USAID/Washington to obtain concurrence prior to initiation of in-country activities. Also, project activities are only launched once the Initial Environment Examination (IEE) and Environmental Mitigation and Monitoring Plans (EMMP) are complete.

Monitoring, evaluation, and learning (MEL) staff will focus on implementing the MEL Plan in close collaboration with project management, the full team, and USAID. The MEL approaches include the indicators, outcome mapping, learning, and evaluation. MEL staff will also assist with the Key Results Reporting, Management Reviews and regular reporting, coordinating closely with the project management team.

Innovate FP is committed to supporting USAID's goal of helping countries move toward self-reliance. This workplan includes two primary efforts to support this goal: 1) research capacity strengthening of our partner institutions and investigators in low- and middle-income countries (LMICs); and 2) development of contraceptive technologies that have the potential to enhance family planning method choice and create health systems savings for LMICs. In Year 1, we selected LMIC-based sites and partners to contribute to design and to implement the planned research program, which includes human-centered design and acceptability studies as well as clinical trials. As we engage with these potential partners, we will assess their capacity needs and look for opportunities for the Innovate FP project to seamlessly incorporate capacity development and strengthening into the partnerships. In addition, as issues arise under the Rapid Response mechanism, we will make every effort to work directly with field-based partners in order to build capacity to respond locally.

The refined and new technologies that are the focus of Innovate FP will both expand contraceptive options and have the potential to reduce costs for countries. For example, DMPA XT would provide an option of fewer doses per year and fewer visits to health facilities for over 40 million women worldwide who currently use injectable contraception. A biodegradable implant would reduce the removal requirement and therefore the need for trained personnel,

supplies, and equipment compared to current contraceptive implants. The contraceptive microneedle patch, as a self-administered method with no biohazardous waste and a target duration of 3 to 6 months, has the potential to enhance self-care and reduce health systems costs when compared to many other methods.

***Year 3 Workplan:*** The project management team will continue monitoring activity budgets and expenditures along with activity milestones. We will continue to have internal Innovate FP project leadership meetings to discuss implementation, challenges, and necessary adjustments. Our team will submit reports as per the award and upon requests from USAID. We will be in regular communication with USAID via meetings and email.

In Jan. 2021, Innovate FP submitted a draft Gender Analysis and Social Inclusion (GESI) Literature Review to USAID with the goal to better understand potential gender and social inclusion-related considerations for contraceptive technology research and development. FHI 360 and USAID held a meeting to review the plans and FHI 360 incorporated comments from USAID on the GESI strategy, for which USAID provided approval in Apr. 2021. Our team provided an update on implementing the strategy recommendations to USAID in Sep. 2022. After discussion with USAID, we propose to expand our work in this area.

For ongoing Innovate FP activities (such as the DMPA-XT clinical trial), we will consider incorporating the following strategies when feasible. For activities that are currently being implemented, there are timeline considerations and ethics and regulatory reviews and approvals required for document revisions. We may be able to incorporate some strategies in future amendments. For upcoming projects, we aim to integrate applicable strategies during the development process.

Below describes our plans related to research followed by Innovate FP specific project plans. To achieve the plans for both expanded inclusion of gender/sexual minorities and persons with disabilities into contraceptive clinical research, a dedicated staff person with relevant background in gender, social inclusion, and preferable clinical trial research will be required. This person will work with study teams to define GESI goals and define specific project inclusion plans.

**Research:**

Currently there are a few regulatory directives or guidances on inclusion of the LGBTQIA+ community and persons with disabilities in contraceptive R&D clinical trials. The NIH Revitalization Act of 1993 called for increased inclusion of women and racial and ethnic minority groups in federally funded clinical research. The purpose of this Act was to ensure the generalizability of results within these populations; however, these groups remained underrepresented in clinical research. In 2020, FDA published a guidance called “Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry” which provided some useful, practical guidance for the topic. The guidance was intended to encourage researchers to broaden eligibility criteria and adopt more-inclusive enrollment practices to improve the quality of studies, i.e., increase generalizability of study results. The guidance does not address the LGBTQIA+ community, but does include persons with disabilities, and there are fundamental principles that can be extrapolated to both groups. Several Institutes at NIH, including the Institute on Minority Health and Health Disparities (NIMHD) are studying and addressing issues related to diversity

and inclusion in clinical trials through a variety of initiatives and educational materials. If opportunities arise under Innovate FP, we may adapt these NIH materials as appropriate. We will look to integrate these materials into overall FHI 360 systems/research SOPs/and upcoming studies that leverage or are related to Innovate FP work, such as our Gates funded awards. Lastly, Institutional review boards (IRBs), such as WCG (which serves as a central IRB National for some of our trials) are also providing a lot of practical and more forward-thinking guidance on inclusion of these underrepresented groups which are very relevant to our contraceptive R&D programs.

***Gender and sexual diversity***

As part of addressing this topic adequately within new clinical research projects or future protocol amendments, we propose developing an internal work instruction or SOP to guide research teams in incorporating inclusive language within study documents such as clinical research protocols, data collection forms, recruitment materials and informed consents. We will adapt from the existing WCG IRB guidance document, "Making Clinical Research Inclusive: Strategies to Include the LGBTQIA+ Community in Research Trials" and other resources, as appropriate, to assist in development of these documents. To ensure adequate inclusive language, we will also build review of appropriate language into our quality control reviews for study documents and assign a specific FHI 360 staff member with expertise in DEI to review documents prior to finalization to ensure language is inclusive.

For study documents, there are several ways to establish inclusive language including:

- Review and revise demographic data collection to distinguish between sex and gender, and when possible, include questions in regard to both. However, these questions should also be discussed with local investigators implementing the studies to ensure they are culturally appropriate and will not result in any potential harm to the participant in disclosing this information.
- For contraceptive studies, use gender-neutral language.
- For recruitment materials, include images/photos that depict diverse people (e.g., clothes, race, mobility, relationship structure) and more inclusive language regarding sexual activity, when applicable.

In addition to incorporating inclusive language, we will also review and adapt our study practices as feasible to better reach LGBTQIA+ populations and allow their full access to research participation. This will involve adapting FHI 360's Gender, Sexuality, and Sexual Orientation training manual, developed under the USAID Open Doors project in Zambia to improve stigma-free, gender-affirming care for LGBTQIA+ populations clinical trial staff. To track our progress in expanding access to, and inclusion of, gender and sexual minority populations in our studies, we will include numbers of LGBTQIA+ -identifying individuals as part of routine recruitment tracking, as appropriate. Finally, we will explore appropriate ways to incorporate sub-group analyses to identify potential differences in study outcomes among gender and sexual minority groups.

***Persons with disabilities***

People with disabilities are often excluded from clinical trials for a variety of reasons including:

- Trial design and recruitment strategies may exclude people with disabilities due to things like confounding conditions.
- Cost and resource constraints which may include accessibility barriers, such as limited access to transportation to and from research centers.
- Inability to access or read recruitment and consent forms and complete self-administered study forms and questionnaires.

We aim to address some of these barriers for future research studies. We can adapt our quantitative and qualitative research designs to facilitate inclusion of people with disabilities. Specifically, we can:

- Provide additional review of study protocols to align with the Universal Design of Research (UDR) approach. The UDR framework approach has been used to promote inclusion of persons with disabilities in research studies by:
    - Removing disabilities from eligibility exclusion criteria, as appropriate
    - Using various methods (e.g., visual, verbal, etc.) to recruit participants with diverse needs
    - Providing study instructions and instruments to accommodate people with disabilities (e.g., providing materials in Braille)
    - Providing multiple options for study participants to complete study instruments

For research on products with self-administration, we will include questions around access for users with disabilities.

We propose to include additional disability training for FHI 360 staff and potentially clinical site staff, specifically to increase awareness and strategies to facilitate recruitment, retention, and participation of study participants with disabilities in our clinical trials.

Further we can consider adding more resources to accommodate the study participants within our clinical study site budgets (e.g., transportation).

**BDI Acceptability:**

The BDI User Preferences study included some GESI/DEIA-related questions as part of data collection efforts in Kenya and Senegal. Data collection is complete in Kenya and responses to these questions were somewhat limited. Data collection in Senegal is expected to commence in November 2022 and we will encourage the study team to ensure these questions are sufficiently covered including appropriate probes.

Some example questions:

- “How might clients from different underrepresented groups receive these new methods [BDI products]? (Probe: clients from the LGBTQIA+ community and those living with disabilities)”

- "How do you think clients will feel about this [18 month] duration? Why is that? How might this impact clients with disabilities? What might the advantages or disadvantages be?"
- "Generally, do you think women in the community would use these new methods?
    - a. [If yes] – which category of women would prefer using the new methods? Why them? (Probe for age, culture inclination, marital/relationship status, with/without children, women with disabilities, individuals in the LGBTQIA+ community)"
- "Are there individuals you think should use the new methods? Are there those you think shouldn't? Why? Describe them in detail (probe for age, relationship status, with/without children, married/unmarried, with/without disabilities, LGBTQIA+)."

**CIMC:**

In the expert consultation on contraceptive-induced menstrual changes (CIMCs) in clinical trials we are convening in Jan. 2023, consensus recommendations about improvements in collection and analysis of CIMC data will be developed. In this meeting, we will include a presentation on inclusive language and clinical trial practices around gender and sexual minority populations prior to the consensus-building process to guide the recommendations to be inclusive. These recommendations will then be published and disseminated widely, including highlighting this inclusive language and clinical trial best practices.

**Rapid Response:**

Future documents that the Rapid Response team produces or contributes to (e.g., handbook updates, product briefs, journal articles, etc.) will include inclusive language.

**Hormonal IUD:**

Through FHI 360's position as Co-Secretariat of the Hormonal IUD Access Group, we will seek opportunities to embed a GESI lens in scale up activities. For example, in the revised Global Learning Agenda (GLA), there may be opportunities to understand potential to reach transgender and gender expansive people seeking amenorrhea to reduce gender dysphoria. Further, through a separate grant from the Bill & Melinda Gates Foundation, FHI 360 will be conducting research to understand effective implementation strategies and user experiences as hormonal IUD introduction moves from pilot studies to broader scale-up. We will seek to ensure that protocols developed under that grant employ inclusive language around gender identity and sexual activity.

## *Appendix 1: Innovate FP Year 3 Budget and Estimated Life of Project*

Redacted.